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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,572	05/11/2005	John Arthur Hohneker	ON/4-32752A	4460

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,572	HOHNEKER, JOHN ARTHUR	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-10 and 12-13 are pending.

Claims 1-10 and 12-13 are rejected.

Information Disclosure Statement

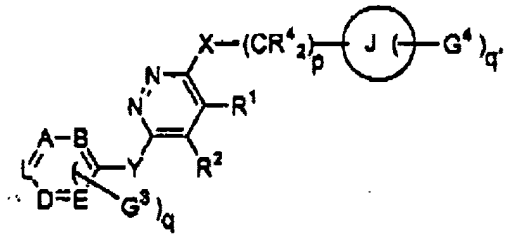
The information disclosure statement (IDS) submitted on 28 November 2005 has been acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the pharmaceutical formulation of 4-pyridylmethyl-phthalazine derivatives to treat cancers of breast and colon as described



by Bold et al (see 103 rejection) does not reasonably provide enablement for the treatment of all types of mesothetheliomas with all variational substitutions of 4-pyridylmethyl-phthalazine derivative. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art

See below:

In the instant case, applicants are claiming a method of treating all types of mesothelioma in a mammal to alleviate the pathological effects of any and all types of mesothelioma diseases (see above listing claims), a pharmaceutical formulation containing a therapeutically effective amount of 4-pyridylmethyl-phthalazine derivative useful for the treatment and/or amelioration of mesothelioma and the manufacture of a medicament for the treatment of any and all mesothelioma (see claim 10).

1) Nature of the invention.

The nature of the invention is directed to the method of treating a mammal with mesothelioma, comprising administering the instant pharmaceutical composition to a patient (mammal) in need thereof. As stated, however, claim1 recite that any or all-mesothelioma conditions or diseases is/are intended.

A. Treatment by Mesothelioma type

There is no one particular anticancer agent that is effective for all forms of mesothelioma cancer. As discussed below, (see Gura and Johnson et al), Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make. Not all the variation of the above compound by Bold et al treat all forms of cancer. Based on the substitution, the effect of the compound will vary with the type of mesothelioma treated. For example pleural mesothelioma is of two kinds: (1) diffuse and malignant (cancerous), and (2) localized and benign (non-cancerous.) While the great majority of mesotheliomas are in either the pleura or the peritoneum, malignant mesotheliomas sometimes occur in other parts of the body, including the testicles (a variety of peritoneal mesothelioma) and the heart (a variety of pleural mesothelioma.) These are also caused by exposure to asbestos fibers. (Kittle: Mesothelioma Diagnosis and Management, Year Book Medical Publishers, 1987)

While the state of the art is relatively high with regard to the treatment of cancers with specific agents, for a compound or genus to be effective against cancer or a disease associated with cancer generally is contrary to medical science. Thus a

considerable amount of invivo and invitr testing is required before the agent can be considered for a particular type of disease.

B. Chemotherapy

Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, more recently with regards to unpredictability, Johnson et al (British J. of Cancer 2001, 84(10) 1424-1431) teaches the use of 39 agents invivo activity in a particular histology in a tumor model did not closely relate to activity in the same human cancer. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary

skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between all the diseases claimed as capable of being treated by compounds of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of inflammation. Also Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine composition could be predictably used as an anti-cancer agent for all cancer therapeutic strategies as inferred by the claim and as contemplated by the specification. Further, the refractory nature of cancer to drugs is well known in the art

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of mesothelioma disease to be treated, and then determine which of the thousands of compounds would be suitable for said treatment and/or prevention.

4) Level of predictability in the art.

The art pertaining to the treatment of all cancerous conditions remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art. Firstly, for a compound or genus to be effective against cancer or a disease associated with cancer generally is contrary to medical science. Cancer is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the cancer reaction. Accordingly, treatments for cancer are normally tailored to the particular type of of mediator present, as there is no, and there can be no "magic bullet" against all cancer related diseases generally.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is nowhere found in the specification. However, the gap between *in vitro* activity and *in vivo* utility is large enough to warrant thorough and compelling *in vivo* or clinical data.

6) Existence of working examples.

As discussed above, no working example is found. Applicant's omission of working examples does not enable one of ordinary skill in the art to treat the numerous amounts of diseases encompassed by the instant invention.

7) Breadth of claims.

Claim1 is extremely broad due to the vast number of possible diseases encompassed by the instant invention.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of any disease. As a result necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

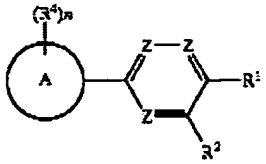
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Halbrook et al., US 2002/0165218 in view of Dumas et al., WO 01/10859 taken with Bold et al US 6,258,812.

Halbrook et al teach the instant claim 1 treating mesothelioma (see ¶ 0149)

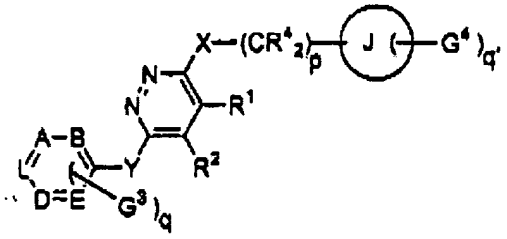


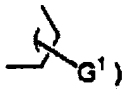
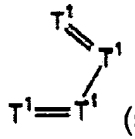
administering a DNA-PK (DNA –protein kinase) inhibitor,

structurally similar to the claimed compound recited in claim 2 in a pharmaceutically acceptable salt (see ¶ 0025) as in claim 12 wherein the salt is the succinate salt (see¶ 0168) as in claim 13. The reference also teaches the current claim 4 the mesothelioma is peritoneal (see ¶ 0149) wherein the warm-blooded animal is human (see ¶ 0046) as in claim 5.

As to claim 6 the dosage range is from 0.1-1000 mg/day. The above-mentioned reference also teaches the drug is used in combination with surgery (see ¶ 0135).

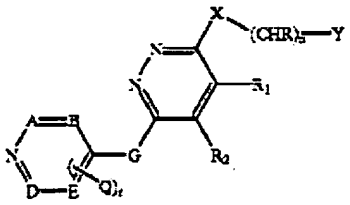
Dumas et al teach a compound structurally similar



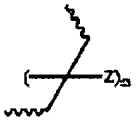
with that of the claimed invention recited in claim 2 (see page 4 lines 5+) wherein R^1 and R^2 are (i) lower akyl and (ii) together form a bridge  , (iii)  (see page 8 lines 5+). T_1, T_2, T_3 and $_4$ are nitrogen (see page 4 lines 19+) and in each case CH and the binding is achieved via T_1 and T_2.

With regard to claim 3 the compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine is an obvious variation of the substituents (see examples 1-4 pages 38-40).The reference also teaches the dosage range of the compound to be from 1300 mg/day (taken into account that 0.1-200 mg/kg per day, average weight to be 65 kg) as in claims 6 –8).

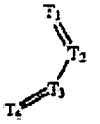
Bold et al teach the current claim 2



wherein r is 0 to 2, n is 0 to 2; m is 0 to 4; R_1 and R_2 (i) are in each case a lower alkyl, or (ii) together form a bridge in subformula I*



(I") or (iii) together form a bridge in subformula I"*



and the (see col. 3 lines 1-65+). With regard to claim 3 the compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine is recited (see col. 13 lines 61+) treating protein kinase inhibition and angiogenesis.

Although, the Halbrook et al reference did not explicitly teach the exact compound as recited in the claim invention, it would have been obvious to one of ordinary skill in the art to combine Halbrook et al with that of Dumas et al taken with

Bold et al, switch the compound taught by Halbrook et al with either Dumas et al or Bold et al use in the treatment of mesothelioma in humans. One of ordinary skill in the art would have been motivated to use the compound taught by either Dumas or Bold to treat mesothelioma because they are all tyrosine kinase inhibitors, and Halbrook has shown that a tyrosine kinase inhibitor structurally similar to Halbrooks compound is used in the treatment of mesothelioma.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher S. Low

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3/14/06